hours in the viscus, although there was no actual organic stenosis of the pylorus, as the results of the duodenal bucket test showed. In all of the cases the stomach was considerably dilated and atonic.

The duration in each instance was somewhat longer and the degree of physical deterioration was not so marked as is usual in persons suffering with carcinoma of the stomach for the same length of time.

In most of the cases the blood showed a high lymphocyte and eosinophile count, with a moderate degree of chloroanemia.

Notwithstanding the low peptic power, the appetite in all but one case was keen and the food was relished.

Vomiting occurred at some time during the course of the illness in all my cases. There was nothing suggestive in the condition of the bowels. On examination of the abdomen of these cases the recti showed constant tendency to go into marked spasm on palpation. For this reason a tumor mass may not be so easily recognized as it would be in carcinoma of the stomach.

THE VALUE OF TYPHOID VACCINES IN THE TREATMENT OF TYPHOID FEVER.

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Following such phenomenal success in the prophylactic use of typhoid vaccines it is but natural, with a logical theoretical basis, that they should also be tried for the cure of typhoid fever. The large number of typhoid cases admitted annually to the Pennsylvania Hospital have been utilized by us as a favorable basis for an investigation of the value of such a procedure. While the benefit, of course, is less striking than that following its prophylactic use, we are gratified to be able to report distinctly favorable results from three years' observation on cases at the Pennsylvania Hospital. In the later cases, whether from the larger doses used or the more experience acquired, the results have been so much more favorable that we feel justified in recommending the proper use of typhoid vaccines as a specific and valuable form of treatment of this very important disease.

In 1912 Drs. J. C. Wilson and J. Walker treated 44 cases with a commercial stock antityphoid vaccine, and have been good enough to give us their hitherto unreported material to further this study. Two years ago we began another series, treated with a vaccine prepared by Dr. Richardson from the Rawling's strain, the same as that used by both the English and American armies. In order to give the procedure as critical a test as possible, the vaccine was given only to the severer cases. Our tabulated figures proved but little better for the vaccinated than the unvaccinated. Deceived at first by our method of selection, it was not until we had carefully analyzed the individual cases that we realized how constant the improvement after vaccination had been. Thus stimulated we began again last year with a vaccine differently prepared and in larger doses. Unfortunately we were prevented by extraneous circumstances from applying the excellent results obtained in this series to more than 16 cases, before the epidemic abated, but hope later to supplement this study with other statistics. These three series, aggregating 93 cases, form the basis of this study.

HISTORY. The history of the curative use of typhoid vaccines is brief. In 1893, Fraenkel[1] treated 57 severe cases with a vaccine prepared much as are those of today. Typhoid bacilli, grown for three days in thymus bouillon, were killed at 63° C., tested for sterility, and injected subcutaneously (dosage not given). Although he noted a marked improvement and recommended its further use, his work apparently escaped notice, and no further attempts were made on such lines for fifteen years. In 1908 Pescarolo and Quadrone[2] inoculated 20 cases of typhoid fever with living attenuated organisms in small doses and, in spite of a rather severe reaction, reported favorable results.

With an antityphoid serum (prepared from horses immunized with a toxin from typhoid bacilli grown on special media) Chantemesse[3] reduced the mortality from 17 per cent. of untreated cases to 4.3 per cent. in 1000 cases thus treated. According to Semple[4] it is generally accepted that Chantemesse's serum "acts as a typhoid vaccine, owing to the probability that it contains the bacterial elements originally injected into the horses which supplied the serum." In this summary we have not taken account of vaccines prepared by methods differing from Wright's, such as Renaud's irradiated or Besredka's sensibilized vaccines. Results of treatment with these methods are given by Netter.[5]

With the promulgation of Wright's opsonic theory and his treatment by vaccines came a renewed interest in typhoid therapy. In January, 1909, Watters and Eaton[6] reported the results of 30 cases thus treated, the first routine curative use of typhoid vaccine after Fraenkel. The next month Captain Smallman,[7] at Leishman's suggestion, described 36 cases in the Indian army treated with doses ranging from 100,000,000 to 350,000,000 bacteria, prepared according to Wright's method. There were three deaths, no relapses, and the patients seemed less toxic. With perhaps unconscious humor he says, "It was no uncommon thing to go into the ward when full (sic) and find nearly every patient quietly and comfortably sleeping."

Since then over 1800 cases have been reported by about forty observers, the great majority with favorable results. Generally speaking the larger the dose the better the results obtained. Thus Sadler,[8] using the very small dosage of 1,000,000 and 2,000,000 had fourteen deaths in 92 cases; whereas Meakins and Foster, using one to three doses of 1,000,000,000 to 1,500,000,000, had but one death in 42 cases. The average duration of fever in this series was reduced from thirty-seven to twenty-eight days and complications occurred in 5 per cent. (versus 42 per cent. unvaccinated); relapses in 2.4 per cent. (versus 13 per cent. unvaccinated). To some authors it is doubtful if doses under 50,000,000 produce sufficient effect, and yet Watters and Eaton,[9] with doses averaging 25,000,000 to 30,000,000 reported favorable results in 69 cases (2 deaths, and 6 relapses). In the largest single series reported, Petrowitch,[10] at Uskub, reduced the mortality of 460 cases to 3.2 per cent. as compared with 8 per cent. of 220 unvaccinated cases. He used one to three doses of 20,000,000 each of vaccine supplied from the English army. In Semple's[11] 60 cases there were only 3.3 per cent. each of death and relapses, the dosage being usually four to six doses of 6,000,000 to 50,000,000 in the earlier cases, and of 50,000,000 in the later, and he would now recommend even larger doses.

The latest report by Captain MacArthur[12] emphasizes the importance of early treatment. In 63 cases of his series there were 2 deaths (3.1 per cent.), 2 relapses (3.1 per cent.), and 5 other complications (7.9 per cent.), but all of these occurred in the 29 cases vaccinated in the "unfavorable stage" (after the tenth day).

Less favorable results have been reported by M. W. Richardson,[13] using a dosage of 10,000,000 to 100,000,000 on 28 cases. He found that the results were "not striking," except that there was only one relapse as against 10 relapses in 77 unvaccinated cases. Horner[14] found unsatisfactory results with 40 vaccinated cases and 95 unvaccinated controls. With an average total dosage of 516,000,000 the mortality of the vaccinated was 10 per cent. as opposed to 11.5 per cent. of the unvaccinated. Relapses, 20 per cent.; unvaccinated, 11.5 per cent.; complications, 55 per cent.; unvaccinated, 50.5 per cent. The average duration of fever was twenty-four days; unvaccinated, twenty-three days. Although there were no deaths in Nichols'[15] 11 cases, 2 relapses and 2 prolonged fevers made him feel that "the results were quite inconclusive."

This involves less than 5 per cent. of the total number, however, and in the other 95 per cent. the results have been distinctly favorable. Even such a difficult condition as typhoid osteomyelitis lasting a year has been cured in a few weeks by the use of vaccines

STATISTICS OF VACCINE THERAPY.

Author.	No. Cases.	Deaths.	Relapses.	Dosage.	Remarks.
Anders[19]	8	...	1	25,000,000 to 50,000,000	
Callison[20]	38	5	1	500,000,000 to 600,000,000 (repeated every 4th day)	Few complications.
Carr[21]	2	0	0	25,000,000 to 50,000,000 (2 doses)	
Courmont[22]	39	2	8	....	5 per cent. mortality against 20 per cent. unvaccinated.
Duncan[23]	6	0	0	50,000,000 to 1,000,000,000 (1 to 2 doses)	
Elliott[24]	3	0	0	500,000,000 (1 to 2 doses)	
Fletcher[25]	14	2	1	500,000,000 to 1,000,000,000 (1 to 2 doses)	No bad results; all helped.
Grace[26]	6	...	1	....	Cases made milder.
Gray[27]	126	5			
Hollis[28]	51	2	8	10,000,000 to 250,000,000	Less toxic.
Hornor[29]	40	4	22	Average total, 560,000,000	No beneficial effect.
Jewett[30]	15	2	2	25,000,000 to 400,000,000	No effect in 3; some help in 7; marked in 5.
Krumbhaar Richardson Series 1	44	4	3	Average total, 926,000,000	Mulford's Typhobacterin.
Series 2	33	1 (3)	2	Average total, 720,000,000	"Rawling's" killed at 60°.
Series 3	16	0	0	Average total, 1,640,000,000	"Rawling's" killed at 56°; best.
MacArthur[31]	45	2	7	150,000,000 to 1,500,000,000 (3-day interval)	Improved, especially if early.
McLaughlin[32]	13	0	...	50,000,000 to 500,000,000	Good influence.
Martin[33]	2	1	...	30,000,000 (3 to 5 doses)	One well in 2 weeks, other moribund.
Meakins Foster [34]	41	1	1	1,000,000,000 to 1,500,000,000 (1 to 3 doses)	Less fever, toxemia, and mortality than the unvaccinated.
Nichols[35]	11	0	2	....	Average severity.
Oelsnitz[36]	10	0	0	65,000,000 (several doses)	Did better than the unvaccinated.
Petrowitch[37]	460	15	...	20,000,000 (1 to 3 doses)	3.2 per cent. mortality against 8 per cent. unvaccinated.
Ream[38]	17	0	...	50,000,000 to 250,000,000	14 benefited, 3 no effect.
Richardson[39]	28	...	1	10,000,000 to 100,000,000	Fewer relapses, otherwise not striking.
Sacquepee[40]	28	2	...	100,000,000 to 700,000,000 (1 to 3 doses)	Good effect.
Sadler[41]	92	14	...	1,000,000 to 2,000,000 (several)	Benefited.
Sappington[42]	22	3	...	5,000,000 to 50,000,000 (1 to 9 doses)	75 per cent. benefited.
Semple[43]	60	2	2	8,000,000 to 30,000,000 (4 doses) 100,000,000 to 300,000,000	No risk; benefited.
Simons[44]	6	1	...	....	Less severe.
Smallman[45]	30	0	3	100,000,000 to 350,000,000	Good results.
Watters[46]	158	17	8	2,000,000 to 60,000,000	75 per cent. helped, shorter fever.
Watters (quoted)*[47]	316	14	15		
Wilson[48]	6	0	0	250,000,000 to 500,000,000	Less toxic; shorter fever.
Wolverton[49]	12	0	0	50,000,000 to 300,000,000	Beneficial.
Single reports	6	0	0	50,000,000 to 250,000,000	All benefited (some chronic complications).
Total	1806	99	88		35 out of 39 authors (reporting 93 per cent. of cases) found vaccines useful.

* Loc. cit. For these cases, quoted by Watters, no references were given. None are duplicates from the other authorities quoted by us.

(Rosenberger);[16] and a typhoid periostitis of six years' standing cured in two weeks by vaccines (Sharpless).[17] Two of Meakin's and Foster's[18] series, typhoid carriers of eight and twelve years' duration, were also cured by vaccine therapy. The method, therefore, may be said to have successfully passed the stage of "primary laudation," beyond which Osler says, in *Modern Medicine*, that no specific remedy for typhoid had as yet passed. (See accompanying table of cases thus far vaccinated.)

THEORY. The stimulation of antibodies by the injection of dead bacteria in order to lessen the virulence of the attack is theoretically logical, just as is its prophylactic use for the prevention of the disease. A study of the agglutination curve after prophylactic vaccination shows that there is an increase on the fourth or fifth day, which is still further raised on the sixth and eighth day and then slowly drops to normal. Somewhat the same course is followed by the agglutination curve after vaccination during the attack of typhoid fever.[50]* The frequent absence of the Widal reaction until the second or third week shows that the body may take some time to produce the necessary antibodies, and in such cases, if the diagnosis can be made by other means, early vaccination may be of great help in shortening the attack by earlier stimulation to adequate antibody formation. It must be remembered that many strains of typhoid bacilli have very little ability to form agglutinins, while the culture from which our vaccines are made has been picked largely for its value in that direction, and is therefore presumably better than an autogenous vaccine. It is frequently found that a bacillus from a virulent case is poor in agglutination, just as our strain used for vaccination, though strong in agglutinins, is weak in toxic properties.

The natural antibody formation is presumably largely limited to the spleen, lymph nodes, intestines, and places where the typhoid bacilli mainly congregate, and as any body cell may participate in antibody formation it is probable that the subcutaneous injection of the dead bacilli affords new areas for antibody formation, and thus helps to stem the tide of invasion. This appears to be Major Russel's, Leishman's, and Semple's theory of the beneficial action of the curative action of the vaccine in a systemic infection, in spite of Hektoen's[51] experiments on dogs, which tend to show that the tissues at the site of injection of antigen do not take part in the production of antibodies. The "negative phase" of Wright's opsonic work is absent or negligible, according to both Leishman[52] and Russell,[53] and certainly no clinical evidence of its presence is usually seen. In this connection it must be remembered that the rise in temperature that so often follows the injection of adequate amounts of vaccine is no indication of a negative phase, and, further, that the temperature curve is an index of the degree of intoxication, not of the degree of infection or resistance to it.

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* Recent observations by various authors have lessened the value of this evidence by showing that the agglutination and protection curves do not necessarily run paralle .

According to Theobald Smith,[54] "the effectiveness of vaccines applied in the course of acute febrile diseases, such as typhoid and pneumonia, must be accounted for by principles of which experimental medicine has as yet no definite knowledge," and in this predicament we must fall back on clinical and statistical evidence. The crux of the matter, as Semple puts it, is that "vaccines in quantities sufficient to stimulate increased production of bacteriotropic substances can be injected hypodermically into patients suffering from typhoid fever without adding in the least to their toxic condition." We have increasing evidence that the clinical results of such inoculation are favorable.

PREPARATION. The vaccine used during the summer of 1913 was prepared after Wright's method. The cultures were grown on plain agar and suspended in sterile normal salt solution. After shaking and counting the suspension, organisms were killed by a temperature of 60° C. for one hour. The vaccine was made with 1,000,000,000 organisms to each cubic centimeter and 0.3 per cent. of lysol added. The only change in making the vaccine for use during the past year was in killing the organisms. This was done at 56° C. for one-half hour.

ANALYSIS OF CASES.* *Series I.* Forty-four cases were treated with Mulford's Stock Typhobacterin. In this, as in the other series, the treatment of the vaccinated cases was otherwise identical with the unvaccinated cases. The Widal reaction was positive before inoculation in 24 cases and suggestive in 6. Four of the 14 negative cases gave positive blood cultures, and the other 10 gave sufficient clinical evidence to be considered typhoid by Drs. Wilson and Walker. The total dosage varied from 50,000,000 to 1,650,000,000, given in one to five doses. The average total dosage was 926,000,000 per patient. There were 4 deaths, 3 relapses, and 12 complications (5 hemorrhages, 2 perforations, 2 phlebitis, 1 cystitis, 1 periostitis, 1 abscess).

CASE ABSTRACTS. CASE 4.—Male, aged twenty-one years, positive Widal, received only one dose of 100,000,000 on the seventeenth day of disease, a hemorrhage occurred eight days later, followed by double otitis media, mastoiditis, meningitis, and death.

CASE 11.—Male, aged twenty-two years, negative Widal and blood culture. Received 125,000,000 on the twelfth day and 250,000,000 on the sixteenth day. Was very toxic from the start. Hemorrhages. Death on twentieth day.

CASE 32.—Female, aged twenty-one years, positive Widal, 600,000,000 given on twenty-third day; 700,000,000 on twenty-seventh day; 800,000,000 on thirty-first day. Perforated seven days later. Died twenty-four hours after operation. Second perforation found at autopsy.

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* In order to save space, protocols of individual cases will only be given to bring out special points.

CASE 44.—Male, aged thirty-four years, positive Widal, 500,000,000 on fifteenth day; 700,000,000 on nineteenth day. Death three days later, probably from perforation.

Two of these cases, therefore, received very small doses, and on the other two specific treatment was begun at too late a date. Several others, especially where treatment was begun before the tenth day of the disease, showed quick drops of temperature after injection with a short febrile course. (Case 20, nine days fever; Case 24, seventeen days fever; Case 31, fifteen days fever; Case 33, seventeen days fever; Case 41, eleven days fever). Of course it is impossible to predict what the febrile course would have been without vaccination, and it is fair to say that abortive cases appeared among the unvaccinated controls, but not to the extent or degree that was present among the vaccinated. In several unvaccinated cases also these early drops to normal were frequently followed shortly by remissions of temperature.

Series II. The 33 cases in this series were treated with the vaccine prepared by Dr. Richardson from the "Rawling's" strain of typhoid bacilli in total doses varying from 200,000,000 to 1,450,000,000 (one to three doses). The Widal reaction or blood culture was positive one or more times in all cases. In practically all cases a localized redness and soreness of the arm persisted from twenty-four to forty-eight hours. No constitutional aggravation other than a fleeting rise of temperature was noted, and the patients nearly always felt better within a few hours of the injection (Psychic?). There were 3 deaths in this series, but, as the cases abstracts will show, there was only 1 death (3.2 per cent.) (Case No. 66, perforation) in which the vaccine treatment could fairly be considered to have failed, and in this vaccine treatment was not begun until the twenty-sixth day. Of the other two, Case No. 57 had already developed a complicating pneumonia when he was given his first vaccine four days before death, and his death was from pneumonia. The other, Case 59, had recovered from his typhoid, and after ten days' normal temperature, developed lobar pneumonia and died from it. In 170 milder cases of typhoid not getting vaccines, that were treated in the wards during the same period, there were 14 deaths (8.02 per cent.).

In the 33 vaccinated cases there were 2 relapses occurring after vaccination (6 per cent.) (Cases Nos. 65 and 68.) The former is of special interest as the only example in our cases where the vaccine may be accused of having done harm (see Case Abstract). It is of course impossible here to rule out coincidence, and vaccination was begun very late. In the unvaccinated cases there were 16 relapses (9.2 per cent.).

In the vaccinated cases there were 4 complications (12.1 per cent.)

Of these a perforation and a pneumonia have already been considered among the fatal cases. Case No. 52 developed phlebitis and Case No. 67 had a slight hemorrhage, each some days after vaccination. Of the unvaccinated cases 18 were complicated (10.6 per cent.). The average number of days of fever of the vaccinated cases (including relapses and complications) was 36.7 days; of an equal number of lighter unvaccinated cases occurring at the same period 33.7 days. The average temperature of the vaccinated cases, as near as could be determined, was 102.2° F. before vaccination and 101.4° F. after vaccination. The average temperature of the same number of unvaccinated cases was 102.3° F. The temperature variation (taken every fourth hour) was greater in 13 cases after vaccination than before, less in 10 cases, and showed no change in 11 cases. In almost every case a rise in temperature of 1° to 3° was noticed immediately after vaccination. This was followed in *23 out of 33 cases by a distinct fall in temperature that frequently* temporarily reached normal. This was nearly always more marked after the second and third doses than after the first. In some cases it fell steadily to normal, where it remained; in others after falling for twenty-four to seventy-two hours it again rose. Of the 10 cases which were not benefited by the vaccines, 5 (Nos. 49, 54, 55, 58, 60) probably did not receive big enough doses (total dosage between 200,000,000 and 850,000,000), 3 (Nos. 52, 59, 66) were all obviously virulent infectious, and 2 (Nos. 53 and 67) showed no benefit, in spite of adequate dosage (850,000,000 and 1,050,000,000) begun on the eleventh and thirteenth days. In spite of special effort to begin vaccine treatment early, the average day of disease of the first dose was the twenty-first. This is due partly to the type of patient in the ward, partly to the delay necessary to make a sure diagnosis. Of 2 who got their first dose before the tenth day of the disease, one (No. 48) had only fourteen days of fever, the other (No. 55) had twenty-nine days of fever. The average days of fever after the first dose was given was 16.3 days after the last dose 11.3 days.

CASE ABSTRACTS.—CASE 48.—Male, positive Widal. Given 100,000,000 on eighth day of disease (no change); 150,000,000 on twelfth day (temperature rose 1.5°, then dropped steadily until it reached normal in forty-eight hours). Given 400,000,000 on fifteenth day (temperature rose from 98° to 101° for a few hours and returned to normal permanently).

CASE 50.—Male, positive Widal. Given 60,000,000 on tenth day of disease (no change); 150,000,000 on fourteenth day (temperature dropped from 102° gradually to normal); 300,000,000 on seventeenth day (temperature reached normal on next day and stayed there permanently).

CASE 52.—Male. Positive Widal and blood culture. Given 100,000,000 on eighteenth day of disease; 250,000,000 on twenty-first day; 500,000,000 on twenty-fourth day. No appreciable change in temperature occurred after any injection, but a new crop of rose spots were noted after the last dose of vaccine. Recovery after forty-eight days of fever due to a complicating pleurisy and phlebitis. (Note: In the light of later cases, further injections would be indicated in such a case, unless the new crop of rose spots were taken, not as a coincidence, but as an index of the liberation of more living organisms, in which case further specific treatment would be doubtful.)

Case 57.—Male. Positive Widal. After twenty-five days of fever, including 2 remissions and relapses, patient developed another rise in temperature. Two days later 100,000,000 were given, but it was found that the increased fever was due to pleurisy and pneumonia. Three days later 100,000,000 were again given and patient died the same day. (Note: This was not a suitable case for vaccine treatment. While it is impossible to form an opinion as to whether the vaccines contributed to the fatal issue, they certainly are not indicated in such a condition.)

Case 59.—Male. Positive Widal. Given 150,000,000 on tenth day of disease, 400,000,000 on thirteenth day, and 700,000,000 on sixteenth day. But little effect from any dose, though the temperature fell gradually soon after last dose. Temperature became normal on forty-second day. After ten days the temperature was normal, a typical lobar pneumonia developed and proved fatal in four days.

Case 65.—Female. Positive Widal. Given 150,000,000 on thirty-third day, and the temperature dropped quickly to normal on the same day. After three days of normal temperature, 400,000,000 were given. This was at once followed by a rise in temperature which ushered in a relapse of considerable severity, lasting twenty-six days. (Note: In this case the vaccine was given to put a stop to a long-continued mild fever. It is doubtful, in the light of this case, whether such procedure is advisable unless there is further evidence of deficient antibody formation.)

Case 66.—Male. Positive Widal. Given 200,000,000 on twenty-fourth day of disease, 450,000,000 on twenty-seventh, and 800,000,000 on thirty-first day. This case was a very toxic one throughout, and although he seemed benefited by each dose (less toxic and lower temperature), he died on the thirty-fourth day from a perforation.

Case 67.—Male. Two positive Widals. Given 150,000,000 on eleventh day of disease, 300,000,000 on fourteenth day, and 600,000,000 on nineteenth day. The temperature went up and stayed up after each dose. A few days after the last dose a mild hemorrhage occurred. Fever continued for seventeen days after the last vaccine was given. (Note: This case may indicate that if no favorable response is made to the first or possibly the second dose the case may be unsuitable, and further specific treatment should be abandoned.)

CASE 68.—Male. Two positive Widals. Given 150,000,000 on fourteenth day; 300,000,000 on seventeenth day; 600,000,000 on twenty-second day. Drop of temperature after each, reaching normal after twenty-seven days. Seven days later, following increase in diet and permission to get out of bed, a moderately severe relapse started. (Note: This case should be considered as one in which too early increase in feeding caused a relapse in spite of the administration of vaccines.)

CASE 71.—Male. Positive Widal. After forty-three days continuous fever, given 200,000,000 (followed by a quick drop of 3° F.). On forty-seventh day given 400,000,000 (causing greater fluctuations, and drop to normal after several days). On the fifty-seventh day given 600,000,000 (after a temporary rise, temperature became permanently subnormal). (Note: Unless due to coincidence a protracted febrile course was here terminated by vaccines, although the Widal was already positive.) (Compare Case 65.)

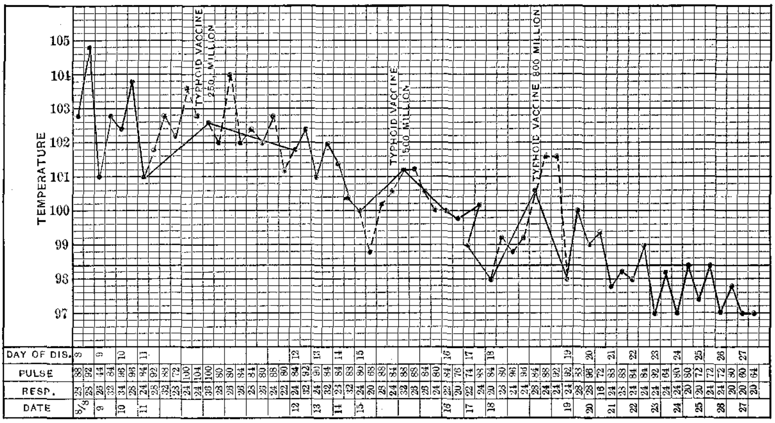

FIG. 1.—Case 83. S. M. Widal positive. Average curative effect of typhoid vaccine. Dotted lines indicate fourth-hour temperature; heavy lines, morning and evening temperature.

CASE 77.—Male. Positive Widal. On sixteenth day of disease given 150,000,000. This was followed by a steady drop to normal on the nineteenth day of the disease. (Note: Unless due to coincidence the effect of a single dose of vaccine is here strikingly shown.)

Series III. Owing to the sudden termination of the typhoid epidemic with the colder weather it was not possible to treat more than 16 cases in this manner. The total dosage ranged between 850,000,000 and 3,350,000,000,* (average 1,640,000,000 in one to five doses). There were no deaths, no relapses, and 1 complication. (Case 84 developed bronchopneumonia after eighteen days' normal temperature.) The average number of days of fever was 21.6, after the first injection 8.3 days, and after the last injection 3.3 days. The average date of the first injection was on the twelfth day of disease. (The difficulty in securing patients early in the disease has already been commented upon.) In only 2 cases was vaccination begun before the tenth day (Cases 92 and 93), and these two showed only fourteen and sixteen days of fever. Either the Widal reaction or blood culture was positive in all (Widal in 14, blood culture in 3). As usual no aggravation was noted after injection and the fleeting rise of temperature, except in 2 cases (Case 87, diarrhea; Case 91, chilly sensations).

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* In three cases where a single dose proved sufficient the amount was naturally smaller.

In the 16 control cases (occurring at the same time) there was 1 death, 1 relapse, 2 complications (hemorrhage and perforation); the average duration of fever was twenty-eight days, and the average date of admission was on the eleventh day of the disease. Thirteen gave positive Widals and 3 suggestive.

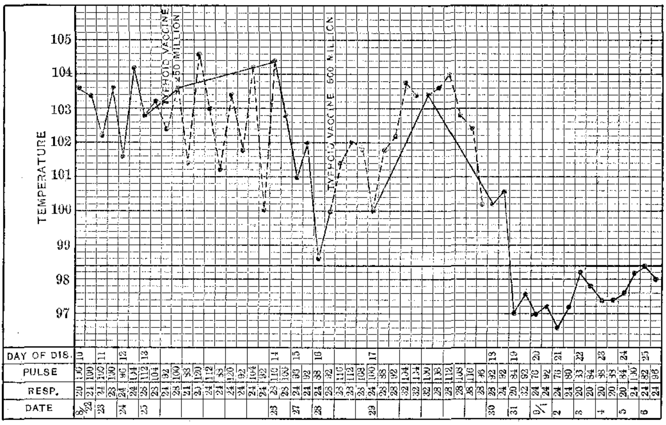

FIG. 2.—Case 85. M. C. Widal positive. More pronounced effect following two injections of vaccine.

CASE ABSTRACTS. CASE 84.—Male, aged forty-five years. Farmer. Positive Widal. Very toxic throughout (stuporous). Was probably sick for two weeks before admission. On nineteenth day (?) received 250,000,000; on twenty-second day, 500,000,000; on twenty-sixth day, 1,000,000,000; on thirty-second day, 800,000,000; on thirty-seventh day, 800,000,000. The last 3 were followed by drops of the temperature to normal, the last time permanently. Patient improved steadily, but still was mentally dull. After sixteen days' normal temperature a relapse began, which ran a mild course lasting eight days.

CASE 87.—Male. Positive Widal. Exhibited a temporary diarrhea and headache after the initial dose of 300,000,000 on the twelfth day of the disease. Given 700,000,000 on fifteenth day and reached normal on same day. After 1,000,000,000 on nineteenth day the temperature rose to 99.2° for twelve hours.

Case 91.—Male. Positive Widal. Had chilly sensations and a rise of 3° in temperature after his only dose of 600,000,000 on the fourteenth day of the disease. His temperature then fell steadily, reaching normal in thirty-six hours, where it remained.

Case 93.—Male. Positive Widal. Given 600,000,000 on sixth day; 1,000,000,000 on ninth day; 1,000,000,000 on twelfth day. But little change after first two doses. After the third dose there was a steady drop of temperature to normal in forty-eight hours, where it remained.

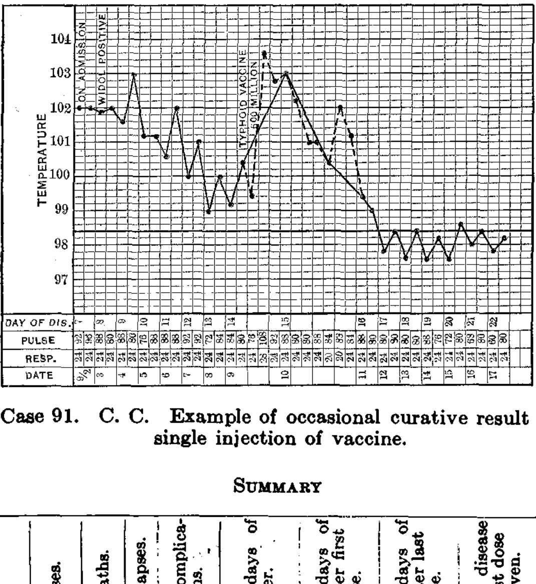

Fig. 3.—Case 91. C. C. Example of occasional curative result following a single injection of vaccine.

Summary

Series.	No. of cases.	No. of deaths.	No. of relapses.	No. of complications.	Average days of fever.	Average days of fever after first dose.	Average days of fever after last dose.	Day of disease when first dose was given.	Average total dose.
1	44	4	3	12	27.4	13.8	6.3	13.0	926,000,000
2	33	3	2	5	36.7	16.3	11.3	21.0	720,000,000
3	16	0	1	0	21.6	8.3	3.3	12.6	1,640,000,000
Total vaccinated	93	7	6	17	25.2	12.8	7.0	15.5	1,095,000,000
Unvaccinated	170	14	6	24	34.7	...	...	...	...

Conclusions. 1. The curative use of typhoid vaccines in the course of typhoid fever in order to stimulate further antibody formation, has a logical theoretical basis, although its mode of action has not as yet been demonstrated experimentally. Practical proof of its value is afforded by the rise in agglutinin curves after such vaccination.

2. The proper use of vaccines in the treatment of typhoid fever has been found clinically to be without harm, and usually to produce beneficial results. It rarely causes any noticeable aggravation of symptoms, beyond a fleeting rise of temperature. Relapses and complications are diminished in frequency, but not prevented. The increase in size of the spleen, noted by others, has not been observed by us.

3. The best results are obtained if the injections are begun early in the disease, especially before the tenth day. A blood culture is more valuable than the Widal test in the early stages. Late in the course of the disease, except in selected cases, the value of vaccines (both theoretically and practically) is more dubious. In the chronic complications of typhoid, such as periostitis and cholecystitis, good results have been obtained from vaccines by other investigators.

4. The contra-indications for vaccine treatment of typhoid are not yet clear. We should hesitate to advocate their use in moribund or very toxic cases, during hemorrhages or suspected perforations, or in such complications as pneumonia or otitis where other microörganisms are involved.

5. The best dosage has also not been determined. Semple, Petrowitch and Watters, and Eaton have had good results with small doses; MacArthur, Fletcher and Meakins and Foster equally good results with much larger doses. While this would indicate to some that the true benefit from vaccines was dubious, we feel that the discordance is due to differences of patients and epidemics, preparation of vaccine, and "personal factors." The dosage must vary within certain limits for each patient, and no cut-and-dried rule should be attempted. The more severe the disease the smaller and more cautious should be the dosage. With our methods of preparation we felt that the best initial dose for average adult was 500,000,000; if this proved to be the proper amount, two or more larger doses were given usually at three-day intervals.

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THE PHYSICAL BASIS OF CHRONIC INFECTIONS AND OF RECOVERY WITHOUT IMMUNITY.[1]

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THE practical application of bacterial vaccine therapy is generally recognized to fall into two distinct divisions. The first comprises the procedures resulting in the formation of specific antibodies or ferments in the tissues—that is to say, the bacteriological diagnosis and the preparation and proper administration of the vaccine. The second division—I think it may be safely assumed that the tissues always respond to the vaccine by producing corresponding antibodies—deals with the distribution of the newly formed antibodies, especially with regard to their relation to the infecting bacteria.

With few exceptions all studies so far reported in vaccine therapy have been limited to the first division of the subject. These researches have been sufficiently thorough to give us a good working knowledge of methods for the preparation of vaccines and their administration.

For certain infections this knowledge has been entirely adequate, but for other diseases the factors essential to success are still obscure. I believe that many if not all the failures will be accounted for only after the second phase of the subject has been thoroughly investigated. Whether a more intimate knowledge will lead to better therapeutic methods or whether it will reveal merely that we have reached an *impasse* is the problem that stimulates the formulation of the following suggestions.

Practically all our knowledge of the cellular pathology involved in the second phase of this subject is due to the work of Sir Almroth Wright. Nothing of importance has been added to his conception

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[1] Read at the first annual meeting of the American Association of Immunologists, held in Atlantic City, June 22, 1914.